This pilot trial will determine whether retroviral-transduced peripheral blood progenitor cells (PBPCs) can be selected and expanded *in vivo* after non-ablative chemotherapy in patients with metastatic breast cancer. It will also examine the feasibility of administering induction high-dose therapy with antimetabolites, followed with consolidation using high-dose single alkylating agent therapy and finally intensification therapy with sequential cycles of very high doses of the natural products (paclitaxel followed by doxorubicin).

Patients will receive induction therapy with antimetabolite agents (methotrexate, leucovorin and 5-fluorouracil) for four cycles. Patients will then receive consolidation therapy with three cycles of high-dose alkylating agents. First, patients will receive two cycles of high-dose cyclophosphamide administered with growth factor support. PBPCs will be harvested during the recovery phase of each cyclophosphamide cycle.

One-half of the cells to be reinfused will be transduced with a retroviral vector containing the gene for the multidrug resistance protein (*MDR1* in vector G1MD) and the other half will be transduced with a vector containing the neomycin resistance gene (NeoR in vector G1Na.40). Both of these vectors have previously been approved by the Recombinant DNA Advisory Committee for PBPC transduction in Medicine Branch protocols.

The next cycle will consist of high-dose single agent thiotepa. Hematopoietic stem cells mobilized and collected during the previous cyclophosphamide cycles and transduced with the retroviral vectors will be reinfused following treatment with thiotepa to augment recovery of bone marrow function. After recovery, intensification with natural product chemotherapy will be administered, consisting of four cycles of paclitaxel given as a 24-hour infusion followed by four cycles of single agent doxorubicin. Peripheral blood mononuclear cells will be monitored following each cycle of paclitaxel and doxorubicin for the presence of the *MDR1* and NeoR transgenes. The ratio of the levels of *MDR1* to NeoR transgenes in peripheral blood will determine whether *in vivo* expansion of the PBPCs containing the selectable *MDR1* marker has been achieved.

This protocol combines several highly active chemotherapeutic agents in an attempt to improve upon response rates achieved with current combinations. Patients who do not wish to participate in the gene therapy procedures will be offered identical chemotherapy in a different protocol.